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Comparative structural and vibrational study of the two low energy conformers of neurotransmitter molecule: Norepinephrine [(R)-4-(2-amino-1-hydroxyethyl) benzene-1, 2-diol]

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A computational investigation of the two lowest energy conformers of norepinephrine has been carried out at the level B3LYP using the basis set 6-311++G**. Out of the 11 possible lowest energy conformers, the two lowest energy conformers have been investigated thoroughly for the optimized geometries, fundamental frequencies, PEDs, APT charges, natural bond orbital (NBO) analysis, MEP, contour map, total density array, HOMO-LUMO energies. The second conformer is energetically at higher temperature by 293 K with respect to the first conformer. The bond angles and lengths do not show much variation while the dihedral angles vary significantly in going from conformer first to the conformer second. Some of the vibrational modes of the benzene moiety are conformation dependent to some extent whereas most of the normal modes of vibration of ethanolamine side chain vary significantly in going from one conformer to the other one. The MEP for the two lowest energy conformers suggests that the sites of the maximum positive and negative ESP change on changing the conformation. The atomic charges have also changed significantly from conformer C-I to the conformer C-II.

Keywords: DFT, HOMO-LUMO, Molecular structure, NBO, Vibrational, IR and Raman spectra

1 Introduction

Neurotransmitters are small molecule and hormone norepinephrine (noradrenaline) is the simplest member which belongs to the catecholamine family of the molecules. The norepinephrine (NE), epinephrine (E), dopamine and serotonin bear neurotransmitter function in the human organism[1]. In the adrenergic neurons of the vegetative nervous system (VNS), this preserves the metabolic equilibrium actively maintained by several complex biological mechanisms that operate via the autonomic nervous system to responsible for the neurotransmission. The E and NE are sympathomimetic drugs used primarily as nasal vasoconstrictors for the local application. NE contains a catechol (ortho-dihydroxyphenyl) ring and an ethanolamine moiety. The side chain of NE is flexible in the catechol hydroxyl groups; exerts a key influence on the conformational landscapes and preference of almost all flexible molecule of biological importance. The conformational analyzes have been done with X-ray analysis, nuclear magnetic resonance and molecular orbital calculations[2-4]. The conformational landscapes have been characterized through high-level *ab initio* computation[5-9] using a combination of laser ablation to transfer the molecule into the gas phase to stabilise its individual conformers. Mourik *et al.*[10] studied the relative stability of the two lowest norepinephrine conformers. Nagy *et al.*[6] performed the theoretical conformational analysis for norepinephrine in the gas phase and in aqueous solution. The conformational analysis was examined for the dopamine and NE in the cationic and di-anionic states by Park *et al.*[11] In d molecular structures of the singly hydrated NE complexes have been explored through a combination of electronic structure computation at the DFT/B3LYP level and mass–selected UV and infrared ion-dip spectroscopy following laser ablation of the neurotransmitter into a freely expanding moist argon jet by Snoek *et al.*[8] These authors[8] also found 11 conformers of the noradrenaline. Benoit *et al.*[12] performed the first vibrational calculation of anharmonic -OH stretch frequencies for the two low energy NE conformers.

In the present work, we have investigated theoretically the optimized geometries, and fundamental

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modes along with their IR intensities, Raman activities and depolarization ratios of the Raman bands of the first two of the 11 possible lowest energy conformers of the norepinephrine molecule at the B3LYP/6-311++G(d, p) level. We have also made the normal modes assignments for the NE molecule which have been made with the help of the vibrational assignments made for related molecules and the computed PEDs for the normal modes of the norepinephrine molecule. The normal modes of NE conformers were compared with the corresponding normal modes of epinephrine, dopamine (DOPA), 1, 2-dihydroxy benzene (1, 2-DHB) and monoisoprpanolamine (MIPA) with the help of animation available from the Gauss-View software[13]. APT and natural charges have been computed for the first two conformers.

2 Geometry Optimization

For the norepinephrine molecule, there are large number of conformers which result due to different orientations of the two hydroxyl groups (-OH) and a monoisoprpanolamine (MIPA) side chain. For the norepinephrine conformers, the molecular geometries have been constructed with the help of the molecular visualization software GaussView 5.0[14] and optimized using the Gaussian 09 package at the B3LYP/6-311++G(d, p) level[13]. To prepare the input structures for the optimization of norepinephrine conformers we have adopted the notations and conventions given in literature[15]. Out of the 11 possible lowest energy conformers the overall lowest energy conformer is C-I. The next one higher energy conformer is with energy 0.00093 eV (293 K) higher with respect to C-I. Thus, at room temperature (300 K) existence of the conformers, C-I and C-II appear to be dominant. These are the conformers observed by Mourik *et al*.[9] We have also computed the vibrational frequencies and related parameters, like the bond lengths, bond/dihedral angles, vibrational frequencies with their IR intensities, Raman scattering activities and depolarization ratio of the Raman bands for the two conformers C-I and C-II. Generally, the unscaled vibrational frequencies at B3LYP/6-311++G** level are larger than the experimental values, so, we have used the scale factors proposed by Rauhut and Pulay[16] for the reasonable frequency matching. To help assign vibrational modes potential energy distributions (PEDs) have been computed using the GAR2PED software. In addition, we have computed APT charges, natural charges, MEP, contour map, total density array, HOMO and LUMO energies in order to understand the physicochemical properties of the norepinephrine.

3 Results and Discussion

In the present work, we have computed the structures and quantities of the spectroscopic interest for the first two lowest energy conformers of norepinephrine and compared the respective quantities.

3.1 Molecular geometries

The optimized molecular structures for the two-norepinephrine conformers with atomic labeling are shown in Fig. 1. The total and relative energies and other parameters of spectroscopic importance of the two conformers are given in Table 1 and 2. The C atom of the side chain directly attached to the ring and all the atoms of the benzene moiety lie in the same plane. All the two conformers have the C_1 point group symmetry. The experimental geometrical parameters for the NE moiety have been taken from the crystal structure data of (-)-Adrenaline, E and MIPA [2, 17-18] for the purpose of comparison. The experimental and calculated parameters of NE, E, and MIPA[@], where differences between the calculated and observed parameters or between the calculated parameters of different conformers are not large which are given in Table 3.

It could be seen from Table 3 that the bond lengths vary at the second place of the decimal in going from one conformer to the other. Therefore, most of the

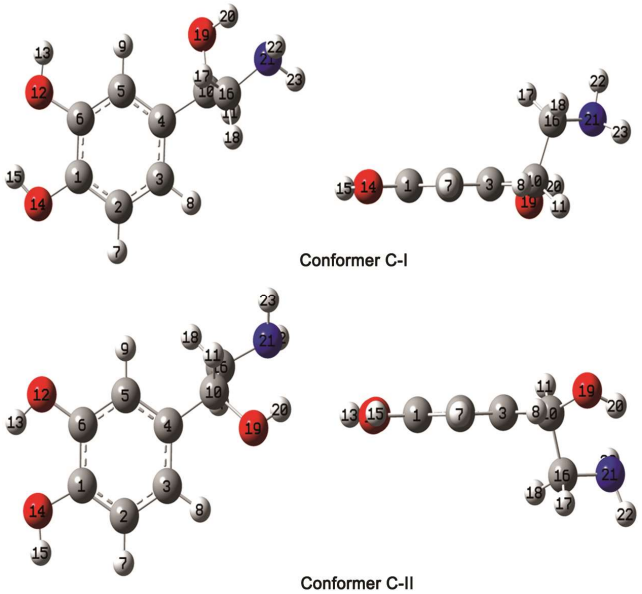

Fig. 1 – Front and side views of two low energy NE conformers.

Table 1 — Total and relative energies of all the possible conformers of norepinephrine.

Conformers	Total energy (Hartree)	Relative energy			
		Hartree	eV	Temp(Kelvin)	kcal/mol
C-I	-585.19988	0	0	0	0
C-II	-585.19895	0.00093	0.025	293	0.582
C-III	-585.19769	0.00218	0.059	689	1.370
C-IV	-585.19763	0.00225	0.061	710	1.412
C-V	-585.19755	0.00233	0.063	734	1.459
C-VI	-585.19748	0.00240	0.065	757	1.505
C-VII	-585.19734	0.00254	0.069	801	1.592
C-VIII	-585.19708	0.00280	0.076	884	1.758
C-IX	-585.19667	0.00321	0.087	1012	2.012
C-X	-585.19656	0.00332	0.090	1048	2.084
C-XI	-585.19509	0.00478	0.130	1510	3.002

Table 2 – Relative molecular properties of NE conformers.

S. No.	Molecular properties	Values	
		C-I	C-II
1	Moment of inertia (a.u. - Å^2)	848.03	843.79
		3735.97	3776.36
		4259.17	4312.50
2	Rotational constants (GHz)	2.128	2.139
		0.483	0.478
		0.424	0.418
3	ZPV Energy(Kcal/mol)	117.504	117.458
4	E_{Th} (Kcal/mol)	124.946	124.936
5	C_V (Cal/mol-K)	45.455	45.510
6	S(Cal/mol-K)	106.797	107.145
7	Dipole moment(Debye)	3.240	2.112

calculated parameters of two NE conformers are nearly same, whereas the differences between calculated and observed parameters[2] have slightly differed. The bond lengths of NE side chain and MIPA corresponding bonds are nearly close to each other. However, the bond lengths C_4-C_{10} and C_{10}-C_{16} are shorter /longer by ~ 0.008 Å going from NE to MIPA. The magnitudes of the computed bond lengths C_1-C_2, C_2-C_3, C_3-C_4, C_4-C_5 and C_5-C_6 of the two conformers lie between C-C (1.54 Å) and C=C (1.33 Å) bond lengths. The bond length C_1-O_{14} is shorter /longer by 0.005/0.010 Å in conformers C-I/C-II and the bond length C_6-O_{12} is shorter by 0.015 Å in conformer C-II, compared to the experimental values[2]. The side chain C_4-C_{10} and C_{10}-C_{17} are found to be larger in comparison to ring C-C bonds due to the conjugation effect.

Similarly, a large number of bond angles shows little conformational changes whereas 12 bond angles show variations ranging from 1° - 5°. The angles α (C_2-C_1-C_6), α (C_5-C_4-C_{10}) and α (C_1-C_6-C_5) show variations of ~ -1°, 1° and 1.3° in going from conformer C-I to C-II. The angle α (H_{17}-C_{16}-N_{21}) of show variation of ~5.6° in comparison to MIPA moiety, whereas the angle α (C_6-C_1-O_{14}) shows a variation of ~ 5.3° from conformer C-I to the C-II. The bond angles α (C_3-C_2-H_7), α (C_2-C_3-H_8), α (C_4-C_5-H_9) and α (C_6-C_5-H_9) show significant deviation from the respective experimental values[2] and also these angles have the variations by ~ 1.1°, 1.3°, 2° and -2.5° in going from conformer C-I to CII, respectively. The bond angles α (C_2-C_1-O_{14}) and α (C_1-C_6-O_{12}) are enhanced by ~4.5° and 5.6° while the bond angle α (C_6-O_1-H_{14}) is decreased by ~ 4.2° in going from conformer C-I to C-II. The computed bond angle α (C_4-C_{10}-O_{19}) of NE conformers is greater than the bond angle in MIPA by ~ 3.4° while this angle is same for E. It is interesting to observe that the geometrical parameters (bond lengths/angles only) related to the NH_2 group do not show significant variation in going from one conformer to the other. It could also be seen from the Table 3 that the dihedral angles associated with the side chain atoms show large variations in going from one conformer to the other.

The bonded and non-bonded lengths r (O….H) in C-I and C-II are found to be 0.966 and 0.962 Å which is well within the limit of H bonding O…..H[19]. The non-bonded angle α(C-O(H)) is expected to be slightly higher(~ 2°) than the bonded angle α(C-O(H)) due to H bonding interaction between the O….H atoms.

All the parameters computed for norepinephrine were also computed for benzene, MIPA, 1, 2-dihydroxy benzene, dopamine and epinephrine to help assign the normal modes of norepinephrine and interpret other parameters.

3.2 APT charges

The APT (atomic polarizability tensor) charge is inferred as the collection of charge tensor and charge

Table 3 – Computed and Experimental geometrical parameters of norepinephrine (NE), Epinephrine (E) and Monoisoprpanolamine (MIPA).

S. No.	Parameters*	NE			E		MIPA	
		Calc. [a]		Expt.[b]	Calc. [a]	Expt.[c]	Calc. [a]	Expt.[d]
		C-I	C-II					
1	r(C_1-C_2)	1.390	1.388	1.39	1.390	1.396	-	-
2	r(C_1-C_6)	1.401	1.401	1.40	1.400	1.405	-	-
3	bonded r(C-OH)	1.365	1.365	1.37	1.365	1.348	-	-
4	r(C_2-C_3)	1.394	1.396	1.39	1.394	1.399	-	-
5	r (C_2-H_7)	1.083	1.086	1.01	1.083	0.90	-	-
6	r(C_3-C_4)	1.396	1.395	1.38	1.396	1.389	-	-
7	r(C_3-H_8)	1.085	1.082	0.96	1.085	1.507	-	-
8	r(C_4-C_5)	1.398	1.399	1.40	1.398	1.381	-	-
9	r(C_4-C_{10})	1.513	1.514	1.52	1.514	0.91	1.521	1.526
10	r(C_5-C_6)	1.388	1.389	1.37	1.388	1.392	-	-
11	r(C_5-H_9)	1.085	1.085	0.95	1.085	0.90	-	-
12	non-bonded r(C-OH)	1.380	1.380	1.38	1.380	1.376	-	-
13	r(C_{10}-H_{11})	1.102	1.103	0.97	1.102	0.75	1.099	1.093
14	r(C_{10}-C_{16})	1.542	1.542	1.52	1.540	1.512	1.534	1.526
15	side chain r(C-OH)	1.421	1.419	-	1.422	1.426	1.441	1.396
16	bonded r(O-H)	0.962	0.962	0.90	0.962	-	-	-
17	non-bonded r(O-H)	0.966	0.966	0.83	0.966	1.02	-	-
18	r(C_{16}-H_{17})	1.093	1.093	-	1.095	0.81	1.105	1.093
19	r(C_{16}-H_{18})	1.097	1.097	-	1.101	0.98	1.096	1.093
20	r(C_{16}-N_{21})	1.471	1.471	-	1.465	1.01	1.462	1.475
21	side chain r(O-H)	0.971	0.970	-	0.971	1.492	0.963	1.139
22	r(N_{21}-H_{22})	1.013	1.013	-	1.016	0.97	1.013	1.017
23	r(N_{21}-H_{23})	1.015	1.015	-	-	-	1.015	1.017
24	α(C_2-C_1-C_6)	119.1	120.1	120.0	119.1	117.4	-	-
25	α (C_2-C_1-O_{14})	120.1	124.6	123.2	120.1	123.0	-	-
26	α (C_6-C_1-O_{14})	120.8	115.3	116.9	120.8	119.6	-	-
27	α (C_1-C_2-C_3)	120.1	120.2	120.0	120.1	122.1	-	-
28	α (C_1-C_2-H_7)	118.6	119.7	126.0	118.6	-	-	-
29	α (C_3-C_2-H_7)	121.3	120.2	114.0	121.2	-	-	-
30	α (C_2-C_3-C_4)	120.9	120.2	121.0	120.9	118.4	-	-
31	α (C_2-C_3-H_8)	119.1	120.4	117.0	119.1	119.2	-	-
32	α (C_4-C_3-H_8)	119.9	119.4	122.0	120.0	122.3	-	-
33	α (C_3-C_4-C_5)	118.8	119.3	119.0	118.8	121.2	-	-
34	α (C_3-C_4-C_{10})	120.6	121.2	123.0	120.6	-	-	-
35	α (C_5-C_4-C_{10})	120.5	119.5	118.4	120.5	-	-	-
36	α (C_4-C_5-C_6)	120.2	120.8	121.0	120.2	119.6	-	-
37	α (C_4-C_5-H_9)	119.2	121.2	118.0	119.2	-	-	-
38	α (C_6-C_5-H_9)	120.5	118.0	120.0	120.6	-	-	-
39	α (C_1-C_6-C_5)	120.8	119.5	119.0	120.8	121.3	-	-
40	α (C_1-C_6-O_{12})	115.1	120.7	119.7	115.2	120.5	-	-
41	α (C_5-C_6-O_{12})	124.0	119.8	120.8	124.0	118.2	-	-
42	α (C_4-C_{10}-H_{11})	108.3	108.3	111.0	108.2	-	109.1	109.5
43	α (C_4-C_{10}-C_{16})	111.8	111.6	-	111.8	-	114.0	112.4
44	α (C_4-C_{10}-O_{19})	110.3	110.4	-	110.3	113.9	106.9	109.4
45	α (H_{11}-C_{10}-C_{16})	108.0	108.0	105.0	108.1	109.4	107.5	109.5
46	α (H_{11}-C_{10}-O_{19})	109.4	109.4	-	109.3	-	109.1	-
47	α (C_{16}-C_{10}-O_{19})	109.0	109.1	-	109.0	105.8	110.2	112.1
48	non-bonded α(C-O(H))	110.2	110.4	112.0	110.2	-	-	-
49	bonded α(C-O(H))	108.2	108.3	111.0	108.2	-	-	-
50	α (C_{10}-C_{16}-H_{17})	108.2	108.1	-	108.3	-	107.8	109.5
51	α (C_{10}-C_{16}-H_{18})	109.6	109.7	-	110.0	-	108.6	109.5
52	α (C_{10}-C_{16}-N_{21})	108.9	108.9	-	109.3	-	111.3	108.1
53	α (H_{17}-C_{16}-H_{18})	107.8	107.9	-	107.5	112.7	106.6	109.5

(*Contd.*)

Table 3 – Computed and Experimental geometrical parameters of norepinephrine (NE), Epinephrine (E) and Monoisoprpanolamine (MIPA). (*Contd*.)

S. No.	Parameters*	NE			E		MIPA	
		Calc. [a]		Expt.[b]	Calc. [a]	Expt.[c]	Calc. [a]	Expt.[d]
		C-I	C-II					
54	α (H_{17}-C_{16}-N_{21})	108.1	108.1	-	108.0	-	113.6	-
55	α (H_{18}-C_{16}-N_{21})	114.1	114.0	-	113.6	-	108.7	-
56	side chain α(C-O(H))	104.9	104.9	-	104.9	-	108.6	103.7
57	α (C_{16}-N_{21}-H_{22})	111.9	111.9	-	109.6	-	110.2	110.4
58	α (C_{16}-N_{21}-H_{23})	111.7	111.7	-	-	-	111.4	111.3
59	α (H_{22}-N_{21}-H_{23})	107.6	107.6	-	-	-	108.0	-
60	δ (C_6-C_1-O_{14}-H_{15})	1.2	-175.5	-	1.2	-	-	-
61	δ (H_8-C_3-C_4-C_{10})	-3.4	3.4	-	-3.2	-	-	-
62	δ (C_{10}-C_4-C_5-H_9)	3.6	-3.3	-	3.4	-	-	-
63	δ (C_3-C_4-C_{10}-H_{11})	38.2	-144.0	-	39.9	-	-	-
64	δ (C_3-C_4-C_{10}-C_{16})	-80.6	97.3	-	-79.2	-	-	-
65	δ (C_3-C_4-C_{10}-O_{19})	157.9	-24.3	-	159.4	-	-	-
66	δ (C_5-C_4-C_{10}-H_{11})	-143.9	37.9	-	-142.1	-	-	-
67	δ (C_5-C_4-C_{10}-C_{16})	97.2	-80.8	-	98.9	-	-	-
68	δ (C_5-C_4-C_{10}-O_{19})	-24.3	157.7	-	-22.6	-	-	-
69	δ (C_1-C_6-O_{12}-H_{13})	-174.7	1.2	-	-175.4	-	-	-
70	δ (C_5-C_6-O_{12}-H_{13})	5.2	-178.3	-	4.4	-	-	-
71	δ (C_4-C_{10}-C_{16}-H_{17})	-56.4	-56.6	-	-57.2	-	-177.1	-
72	δ (C_4-C_{10}-C_{16}-H_{18})	60.9	60.7	-	60.1	-	-61.9	-
73	δ (C_4-C_{10}-C_{16}-N_{21})	-173.7	-173.9	-	-174.6	-	57.8	-
74	δ (H_{11}-C_{10}-C_{16}-H_{17})	-175.4	-175.5	-	-176.3	-	-56.0	-
75	δ (H_{11}-C_{10}-C_{16}-H_{18})	-58.1	-58.2	-	-59.0	-	59.2	-
76	δ (H_{11}-C_{10}-C_{16}-N_{21})	67.3	67.2	-	66.4	-	178.8	-
77	δ (O_{19}-C_{10}-C_{16}-H_{17})	65.8	65.6	-	65.0	-	62.8	-
78	δ (O_{19}-C_{10}-C_{16}-H_{18})	-176.9	-177.0	-	-177.8	-	177.9	-
79	δ (O_{19}-C_{10}-C_{16}-N_{21})	-51.5	-51.6	-	-52.4	-	-62.4	-55.4
80	δ (C_4-C_{10}-O_{19}-H_{20})	159.5	159.2	-	158.0	-	167.7	-
81	δ (H_{11}-C_{10}-O_{19}-H_{20})	-81.5	-81.7	-	-83.1	-	49.9	-
82	δ (C_{16}-C_{10}-O_{19}-H_{20})	36.4	36.2	-	34.9	-	-68.0	28.3
83	δ (C_{10}-C_{16}-N_{21}-H_{22})	157.9	157.9	-	-70.6	-	57.8	159.5
84	δ (C_{10}-C_{16}-N_{21}-H_{23})	-81.4	-81.4	-	-	-	177.7	-78.2
85	δ (H_{17}-C_{16}-N_{21}-H_{22})	40.6	40.6	-	171.7	-	-64.1	-
86	δ (H_{17}-C_{16}-N_{21}-H_{23})	161.3	161.3	-	-	-	55.8	-
87	δ (H_{18}-C_{16}-N_{21}-H_{22})	-79.3	-79.3	-	52.6	-	177.4	-
88	δ (H_{18}-C_{16}-N_{21}-H_{23})	41.4	41.4	-	-	-	-62.7	-

[a] Our work;

X-ray diffraction structural parameters from ref [b-2, c-17, d-18]

*Bond lengths (r) in Å, bond angles (α) and dihedral angles (δ) in degrees (°)

* Dihedral angles with values 0° or 180° are omitted from the Table 3.

flux tensor, conducting to a charge-charge flux model[20]. APT charges have been calculated for the different atomic sites of the NE conformers, E, dopamine, and MIPA at the B3LYP/6-311++G** level and are collected in Table 4. All the C atoms (in the C-C ring) bear negative charges, except C_1, C_6 and side chain C atoms, in conformers C-I and C-II. The C_4 atom has the lowest positive charge in C-II. The carbon atoms C_1 and C_6 of the C-C ring, which is directly attached to the hydroxyl group, bear the highest APT charge in NE, E and also in dopamine while the side chain atoms C_{10} also bears the lowest APT charges in dopamine because of no attachment of electronegative O atom at the site C_{10} in dopamine. The atoms N_{21}, O_{12}, O_{14} and O_{19} posses negative charge and out of these, the O atom has the highest negative charge due to its highest electronegativity. In C-I, O_{14} atom has comparatively the highest negative charge as a consequence of hydrogen bonding between the O and H atoms. Due to direct attachment of an O atom, the atoms H_{13}, H_{15} and H_{20} possess the highest positive charge, in comparison to other H atoms in all the conformers. In the C-I conformer, the magnitude of the charge at the H_{13} atom is the lowest.

Table 4 – Calculated APT charges at various atomic sites for conformers of NE, E, DOPA and MIPA molecules.

Atoms	APT charges				
	NE		E	DOPA	MIPA
	C-I	C-II			
C_1	0.496	0.440	0.499	0.486	-
C_2	-0.055	-0.036	-0.054	-0.047	-
C_3	-0.065	-0.127	-0.066	-0.071	-
C_4	-0.029	0.015	-0.028	-0.015	0.010
C_5	-0.101	-0.090	-0.103	-0.095	-
C_6	0.439	0.481	0.440	0.434	-
H_7	0.052	0.024	0.051	0.052	-
H_8	0.033	0.077	0.034	0.034	-
H_9	0.074	0.053	0.075	0.041	-
C_{10}	0.496	0.497	0.503	0.117	0.532
H_{11}	-0.095	-0.097	-0.096	-0.039	-0.096
O_{12}	-0.727	-0.729	-0.728	-0.719	-
H_{13}	0.296	0.320	0.296	0.294	-
O_{14}	-0.761	-0.752	-0.765	-0.753	-
H_{15}	0.320	0.297	0.321	0.319	-
C_{16}	0.305	0.306	0.287	0.344	0.311
H_{17}	-0.014	-0.014	-0.010	-0.058	-0.122
H_{18}	-0.057	-0.058	-0.071	-0.084	-0.037
O_{19}	-0.670	-0.669	-0.676	-	-0.631
H_{20}	0.320	0.320	0.329	-	0.232
N_{21}	-0.518	-0.519	-0.577	-0.484	-0.494
H_{22}	0.127	0.127	0.111	0.136	0.156
H_{23}	0.134	0.134	-	-0.137	0.140

[#] In unit of e

3.3 Natural charges

The natural (NBO) charges partially come out on the molecular surface, which could be revelatory of the intact chemical attributes of the molecule[21,22]. The charge distributions (in the unit of e) at various atomic sites of the two conformers of NE, E, dopamine, and MIPA have been calculated at the method B3LYP using the 6-311++G** basis set and are given in the Table 5. It could be seen that the carbon atom C_1 and C_6 of the C-C ring directly attached to the -OH group bears positive and nearly same in magnitude in E (~0.0.269 and 0.257 a.u.) as well as dopamine (0.268 and 0.253 a.u.). In conformers C-I and C-II, except the C_1, C_6 and C_{10} atoms, all the remaining 5 carbon atoms possess negative natural charges. The atomic sites C_1, C_6 and side chain atom C_{10} have higher positive APT charges due to attachment of the O atoms. In conformers C-I and C-II, the atom O_{19} has lower/higher APT charges by magnitude 0.006 in comparison to E/MIPA while the atom N_{21} have higher APT charge by magnitudes 0.065 and 0.026 in comparison to E and MIPA. All the hydrogen atoms bear positive charges and the hydrogen atom (H_{13}, H_{15} and H_{20}) directly attached to the electronegative O atoms bears the highest natural charges. The side chain O atom has the highest value in the C-II conformer in comparison to C-I.

3.4 HOMO-LUMO analysis

In the MOs theory, HOMO and LUMO energy level tunings are achieved by varying the conjugation between the donor and the acceptor and play a significant role in investigating the electrical, electronic, and optical properties of molecular systems[23]. The norepinephrine molecule has 90 electrons and hence, it has 45 MOs. The HOMO is held on C-C, C-H, C-O, and C-N bonds in the side chain, whereas the LUMO is located on C=C bonds in the aromatic ring. Therefore, the electronic transition from the HOMO to LUMO suggests the transition from the aromatic part (C=C) to the side chain part (C-C, C-O and C-N) of norepinephrine. The pictorial diagrams of the HOMO and LUMO energy levels for two NE conformers are shown in Fig. 2. The HOMO and LUMO energies of the conformers C-I and C-II (Table 6) are calculated to be -5.949, -5.993 eV and -0.518, -0.521 eV. The energy gap between the MOs is 5.431 and 5.472 eV for the conformers C-I and C-II.

Table 5 – Calculated natural charges[#] at various atomic sites for conformers of NE, E, DOPA and MIPA molecules.

Atoms	Natural charges				
	NE		E	DOPA	MIPA
	C-I	C-II			
C_1	0.269	0.247	0.269	0.268	-
C_2	-0.225	-0.252	-0.230	-0.231	-
C_3	-0.205	-0.203	-0.209	-0.210	-
C_4	-0.062	-0.054	-0.059	-0.048	-0.591
C_5	-0.251	-0.239	-0.255	-0.269	-
C_6	0.257	0.279	0.259	0.253	-
H_7	0.213	0.201	0.215	0.217	-
H_8	0.196	0.229	0.199	0.202	-
H_9	0.227	0.212	0.229	0.207	-
C_{10}	0.123	0.122	0.124	-0.400	0.118
H_{11}	0.161	0.162	0.164	0.207	0.155
O_{12}	-0.716	-0.689	-0.722	-0.708	-
H_{13}	0.477	0.490	0.483	0.480	-
O_{14}	-0.682	-0.723	-0.690	-0.677	-
H_{15}	0.484	0.482	0.489	0.485	-
C_{16}	-0.188	-0.193	-0.184	-0.168	-0.198
H_{17}	0.192	0.195	0.194	0.182	0.150
H_{18}	0.173	0.175	0.178	0.156	0.187
O_{19}	-0.760	-0.763	-0.766	-	-0.754
H_{20}	0.476	0.480	0.479	-	0.454
N_{21}	-0.880	-0.887	-0.715	-0.854	-0.854
H_{22}	0.365	0.368	0.357	0.352	0.358
H_{23}	0.358	0.362	-	0.352	0.351

[#] In unit of e

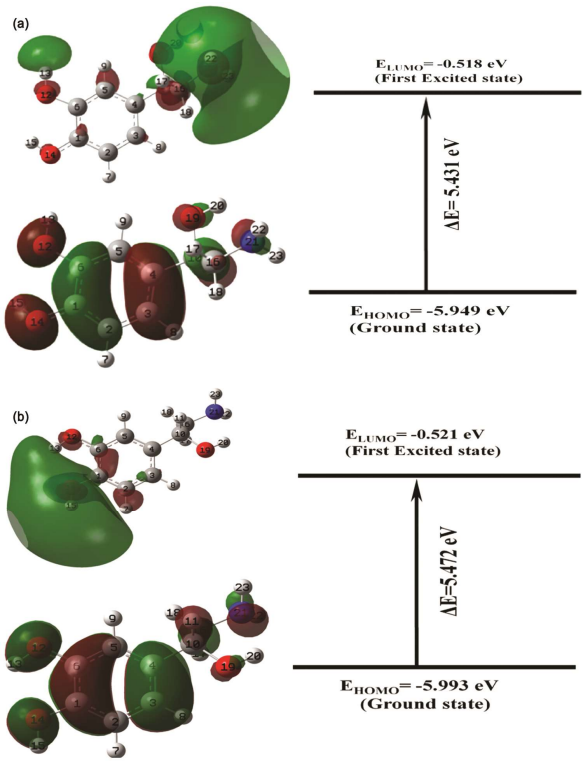

Fig. 2 – Pictorial separation of the electronic energy levels with frontier MOs for NE conformers

The other important parameters of the conformers C-I and C-II, like, ionization energy, electron affinity, hardness, electronic chemical potential and electrophilicity index are estimated to be 5.949 and 5.993 eV, 0.518 and 0.521 eV, 2.715 and 2.736 eV, -3.234 and -3.257 eV and 1.925 and 1.939 eV, respectively. Thus, it is clear that the charge transfer (CT) occurs in the NE molecule and the energy gap between the MOs confirms the bioactivity based on the intra-molecular charge transfer (ICT)[24,25] in the NE molecule.

3.5 Molecular electrostatic potential (MEP) and electrostatic potential (ESP)

The electrostatic potential is a very useful tool to illustrate the charge distributions of the molecules in three dimensions and is fundamentally a measure of the strength of the nearby charges, nuclei and electrons, at a particular position. Hence, the charge distribution within the molecule gives the information about the interaction of the molecule with another molecule[26]. The ESP is invaluable in predicting the behavior of complex molecules and is typically visualized through mapping its values onto the surface reflecting the molecule's boundaries. The ESP is associated with the electron density (ED) and it showed the sites of the nucleophilic reactions

Table 6 – HOMO-LUMO energy value for the conformers of norepinephrine.

S. No.	Parameters	Values (eV)	
		C-I	C-II
1	E_{HOMO}	-5.949	-5.993
2	E_{LUMO}	-0.518	-0.521
3	I.A.	5.949	5.993
4	E.A.	0.518	0.521
5	E_g	5.431	5.472
6	η	2.715	2.736
7	μ	-3.234	-3.257
8	ω	1.925	1.939

Here,
IA: Ionization energy = - E_{HOMO}
EA: Electron affinity = - E_{LUMO}
E_g: Energy gap = E_{LUMO}-E_{HOMO}
η: Hardness = Energy gap/2
μ: Electronic chemical potential = (E_{LUMO}+E_{HOMO})/2
ω: Electrophilicity index = $\mu^2/2\eta$

and electrophilic effect as well as H bonding interactions[27]. In Fig. 3, the areas of low potential, red, are characterized by an abundance of electrons (electrophilic region) and the areas of high potential, blue, are characterized by a relative absence of electrons (nucleophilic regions). The O atoms of NE molecule have a higher electronegativity and have consequently a higher electron density. Therefore, the spherical regions that correspond to oxygen atoms would have a red portion on it. The blue tainted sphere at the top corresponds to the location of the nitrogen atom. The negative area of ESP is responsible for the attraction of proton because of the concentrated ED in the norepinephrine molecule. The MEP, isosurface plot of ESP, ESP contour map and total density for conformers C-I and C-II are shown in Figs 3-6.

3.6 Vibrational assignments

Vibrational assignments of the computed IR and Raman bands of two lowest energy conformers of norepinephrine have been made on the basis of the characteristic modes of the hydroxyl, amino and phenyl groups available in literature[28,29] and the computed modes of E, dopamine, 1, 2–DHB, Bz and MIPA. The forms of the vibrational modes viewed with the help of the Gauss-View 5.0 software[30] and the PEDs computed using the GAR2PED software[31]. The norepinephrine, existing 23 atomic molecules, has 63 normal modes of vibration and possesses a non-planar structure with C_1 point group symmetry. Table 7 contains the distribution of the normal modes of NE molecule. Computed vibrational frequencies

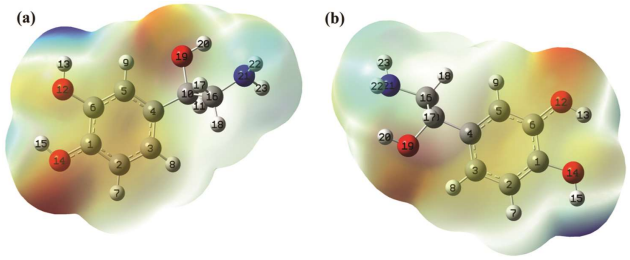

Fig. 3 – MEP for two low energy NE conformers.

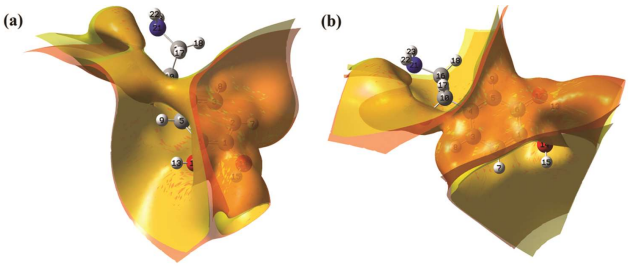

Fig. 4 – Isosurface plot of ESP for two low energy NE conformers.

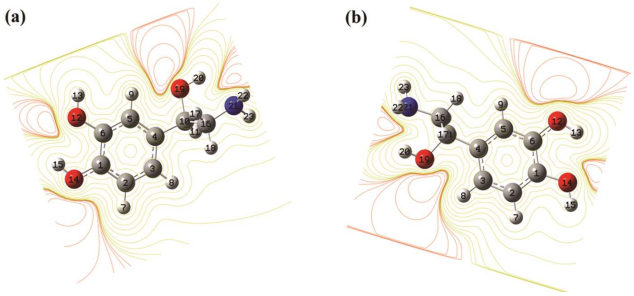

Fig. 5 – ESP contour map for two low energy NE conformers.

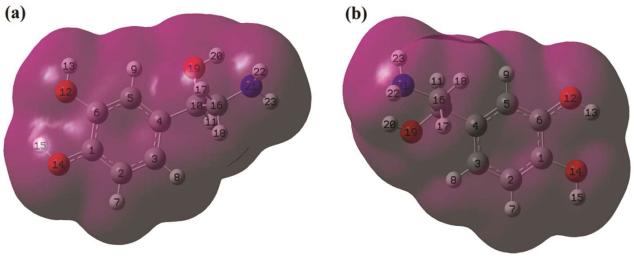

Fig. 6 – Total electron density for two low energy NE conformers.

along with their IR and Raman intensities, Raman depolarization ratios, calculated PEDs and the proposed vibrational assignments for conformers C-I and C-II are expressed in Table 8 and 9. The calculated IR and Raman spectra for the two conformers are shown in Fig. 7 and 8. For the comparison purpose the corresponding scaled and unscaled computed vibrational frequencies of E, dopamine, 1,2–DHB, Bz and MIPA are compared with those of the computed modes of the two conformers of NE molecule in Tables 10 and 11.

Table 7 – Normal mode distribution of norepinephrine.

S. No.	Modes	Total No.	symbol	Groups	No. of modes
1	Stretching	23	ν	C-C	8
				C-H	6
				C-N	1
				C-O	3
				N-H	2
				O-H	3
2	Planer deformation	8	β	C-H	3
				C-OH	2
				C-C	1
3	Ring deformation	6	Φ (R)	R	3
			α (R)	R	3
4	Non-planer deformation	8	γ	C-C	1
				C-OH	2
				C-H	3
5	Twisting	7	τ	C-C	1
			t	C-N	1
				C-O	3
				$^{16}CH_2$	1
				$^{21}NH_2$	1
6	Wagging	2	ω	$^{16}CH_2$	1
				$^{21}NH_2$	1
7	Scissoring	2	σ	$^{16}CH_2$	1
				$^{21}NH_2$	1
8	Rocking	2	ρ	$^{16}CH_2$	1
				$^{21}NH_2$	1
9	Angle bending	5	α	C-OH	3
				C_4-C_{-10}-C_{16}	1
				C_{10}-C_{16}-N_{21}	1
10	Deformation			C_{10}-OH	2
				C_{10}-H_{11}	2
Total No. of modes				63	

The proposed vibrational assignments for the two conformers could be discussed under the following sections:

(i) Phenyl ring (12 modes), (ii) C-H group (12 modes), (iii) O-H/C-OH groups (18 modes), (iv) NH_2 group (6 modes), (v) CH_2 group (6 modes), (vi) C_{10}-C_{16}-N_{21} side skeleton (6 modes), (vii) C_4-C_{10} Linkage (3 modes)

3.6.1 Phenyl ring modes (12 modes)

The phenyl ring of norepinephrine (Fig. 1) has 12 modes of vibration as: 6 ring stretching (ν), 3 planar deformation (α), 3 non-planar deformation (Φ) and modes of the phenyl ring are widely discussed in literature related to the vibrational spectra of benzene derivatives[32,33]. From the Table 10, out of the 6 phenyl ring stretching modes the lowest mode 1 shows a variation of 9 cm^{-1} between conformers C-I and C-II while its magnitude is somewhat decreased for the conformer C-II. In norepinephrine, the phenyl ring breathing mode, corresponding to the benzene ring breathing mode[33] 993 cm^{-1}, is found to have reduced magnitude ~ 783/774 cm^{-1} for the conformers C-I/C-II. The mode 1 of NE conformers and is found to have considerably reduced magnitude compared to benzene, however, it is close to the frequency of the corresponding mode for E, dopamine, and 1,2-DHB. Similarly, the phenyl ring stretching Kekule mode (14) is found at 1327/1323(ν_{44}) cm^{-1} for the two conformers and it appears at higher wavenumber by ~ 50 cm^{-1} as compared to benzene molecule. The mode 14 (Kekule mode) is found to have magnitude very close to that of E, dopamine, and 1, 2-DHB.

The trigonal phenyl ring planar deformation mode 12 is also found its magnitude ~ 1069/1075 cm^{-1} for the conformers C-I and C-II while its magnitude is somewhat increased from benzene (1010 cm^{-1}). The non-planar deformation mode of the phenyl ring corresponding to the mode 4 of conformers C-I and C-II is found to have very close to E, 1,2-DHB, and Bz molecules. The other two non-planar deformation modes of conformers C-I and C-II 16a and 16b have been found at higher magnitudes in comparison to the benzene whereas its magnitudes are found almost same magnitudes of E and dopamine molecules. The planar ring deformation modes 6 (a and b) show decreasing magnitude in going from conformer C-I to C-II. One of the mode 6a is close to the frequency of the corresponding mode for 1,2-DHB and other one mode 6b is close to the E whereas it is found at higher magnitude by ~43 cm^{-1} in comparison to the 1,2-DHB. From the Tables 8 and 9 it should be noted that depolarization ratios corresponding to the Raman bands for all these modes show large variations.

The other ring stretching modes 19 (a, b) and 8 (a, b) corresponding to the mode of NE conformers do not show much variations. In the case of NE conformers, one of the two components 19a and 8a corresponding to the benzene ring stretching modes (1442 &1560 cm^{-1}) are found at considerably enhanced magnitude (~1485 and 1583cm^{-1}).

3.6.2 C-H group modes (12 modes)

There are 12 normal modes corresponding to the three C-H (ring) bonds and a side chain bond. The ring C-H bands corresponding to the stretching, in-plane deformation, and out-of-plane modes lie in the regions 3150-3000 cm^{-1}, 1400-1000 cm^{-1} and 1000-600 cm^{-1}, respectively[32,34-36]. The bonds C_2-H and C_3-H have been coupled strongly for the stretching and out of plane bending modes while the C_5-H bond has been found to be localized stretching and out of plane

Table 8 – Calculated vibrational frequencies and proposed assignments for NE conformer C-I.

S. No.	Frequencies (cm^{-1})		PEDs	Modes
	$^{\$}$Unscaled	*Scaled		
ν_1	34 (5,2)0.75	33	**$\tau(C_4-C_{10})(77)$**	**$\tau(C_4-C_{10})$**
ν_2	81 (1,2)0.72	79	**$\gamma(C_4-C_{10})(27)$**+Φ_2(R)(23)-$\alpha(C_4-C_{10}-C_{16})$(20)	**$\gamma(C_4-C_{10})$**
ν_3	111 (6,0)0.75	109	**$\tau(C_{10}-C_{16})(62)$**-$\tau(O_{19}-H_{20})$(13)-$\beta(C_4-C_{10})$(10)	**$\tau(C_{10}-C_{16})$**
ν_4	179 (8,1)0.73	175	Φ_2(R)(43)+**$\alpha(C_4-C_{10}-C_{16})(13)$**-$\tau(O_{12}-H_{13})$(8)	**α(CCC)**
ν_5	204 (139,1)0.57	200	**$\tau(O_{12}-H_{13})(74)$**+$\tau(O_{14}-H_{15})$(12)	**$\tau(^{12}OH)$**
ν_6	206 (4,1)0.43	201	$\tau(C_{10}-C_{16})$(29)+**$\beta(C_4-C_{10})(27)$**-$\tau(O_{19}-H_{20})$(8)	**$\beta(C_4-C_{10})$**
ν_7	250 (2,1)0.50	245	Φ_3(R)(25)-$\alpha(C_4-C_{10}-C_{16})$(14)+**$\gamma(C_6-OH)(13)$**+$\gamma(C_5-H_9)$(12)	**$\gamma(^6COH)$**
ν_8	259 (9,1)0.23	254	**$\tau(NH_2)(65)$**-$\tau(O_{19}-H_{20})$(21)	**$\tau(NH_2)$**
ν_9	307 (3,0)0.74	300	**$\beta(C_6-OH)(42)$**+$\beta(C_1-OH)$(34)	**$\beta(^6COH)$**
ν_{10}	320 (7,2)0.20	313	**$\alpha(C_{10}-C_{16}-N_{21})(34)$**-$\delta(C_{10}-H_{11})$(8)	**α(CCN)**
ν_{11}	341 (6,3)0.29	333	α_2(R)(24)-$\nu(C_4-C_{10})$(10)-**$\delta(C_{10}-OH)(10)$**+$\gamma(C_1-OH)$(8)	**$\delta(^{10}COH)$**
ν_{12}	401 (1,2)0.46	393	**$\gamma(C_1-OH)(21)$**+Φ_1(R)(19)-$\alpha(C_4-C_{10}-C_{16})$(11)	**$\gamma(^1COH)$**
ν_{13}	412 (70,1)0.61	403	**$\tau(O_{14}-H_{15})(78)$**-Φ_3(R)(10)+$\gamma(C_6-OH)$(9)	**$\tau(^{14}OH)$**
ν_{14}	461 (3,1)0.41	451	**Φ_3(R)(38)**-$\gamma(C_6-OH)$(18)+$\gamma(C_1-OH)$(16)-Φ_2(R)(10)	**Φ_3(R)**
ν_{15}	475 (10,1)0.49	464	Φ_3(R)(15)-**$\beta(C_1-OH)(11)$**+$\beta(C_6-OH)$(8)	**$\beta(^1COH)$**
ν_{16}	549 (3,2)0.14	537	**$\delta(C_{10}-OH)$** (29)+α_3(R)(17)+t(CH_2)(9)	**$\delta(^{10}COH)$**
ν_{17}	578 (9,2)0.70	566	**α_2(R)(18)**-$\beta(C_1-OH)$(13)+$\alpha(C_{10}-C_{16}-N_{21})$(11)+$\delta(C_{10}-H_{11})$(8)	**α_2(R)**
ν_{18}	603 (29,5)0.60	590	**α_3(R)(21)**+$\beta(C_1-OH)$(12)+$\tau(O_{19}-H_{20})$(8)	**α_3(R)**
ν_{19}	613 (95,1)0.62	600	**$\tau(O_{19}-H_{20})(80)$**	**$\tau(^{19}OH)$**
ν_{20}	636 (22,1)0.52	622	**Φ_2(R)(23)**-$\gamma(C_4-C_{10})$(21)-$\gamma(C_6-OH)$(16)-$\gamma(C_1-OH)$(9)	**Φ_2(R)**
ν_{21}	719 (1,1)0.38	704	**Φ_1(R)(56)**-$\gamma(C_1-OH)$(18)-$\gamma(C_6-OH)$(16)	**Φ_1(R)**
ν_{22}	765 (50,15)0.07	749	α_3(R)(15)-**$\nu(C_6-OH)(12)$**-$\nu(C_1-C_6)$(11)-α_1(R)(9)	**$\nu(^6COH)$**
ν_{23}	801 (14,12)0.11	783	$\nu(C_1-OH)$(17)-$\omega(NH_2)$(16)+**$\nu(C_1-C_6)(13)$**-α_1(R)(9)+$\nu(C_1-C_2)$(8)	**$\nu(C_1-C_6)$**
ν_{24}	823 (31,1)0.19	806	$\gamma(C_2-H_7)$(25)+**$\gamma(C_3-H_8)(25)$**-$\omega(NH_2)$(18)	**$\gamma(C_3-H_8)$**
ν_{25}	827 (60,8)0.12	809	**$\omega(NH_2)(22)$**+$\gamma(C_3-H_8)$(16)+$\gamma(C_2-H_7)$(15)+$\nu(C_{10}-C_{16})$(8)	**$\omega(NH_2)$**
ν_{26}	876 (18,2)0.20	858	**$\gamma(C_5-H_9)(67)$**+Φ_1(R)(14)	**$\gamma(C_5-H_9)$**

(*Contd.*)

Table 8 – Calculated vibrational frequencies and proposed assignments for NE conformer C-I. (*Contd.*)

S. No.	Frequencies (cm^{-1})		PEDs	Modes.
	$Unscaled	*Scaled		
ν_{28}	940 (1,0)0.15	920	**γ(C_2-H_7)(43)**-γ(C_3-H_8)(39)	**γ(C_2-H_7)**
ν_{29}	966 (5,7)0.40	946	**t(CH_2)(26)**+ρ(NH_2)(25)+ν(C_{10}-C_{16})(14)	**t(CH_2)**
ν_{30}	978 (28,4)0.35	958	**ν(C_4-C_{10})(14)**-ν(C_6-OH)(13)+ν(C_4-C_5)(13)+ν(C_3-C_4)(10)	**ν(C_4-C_{10})**
ν_{31}	1056 (22,12)0.23	1008	**ν(C_{16}-N_{21})(75)**	**ν(C_{16}-N_{21})**
ν_{32}	1100 (35,5)0.37	1050	**ν(C_{10}-OH)(49)**-ν(C_{10}-C_{16})(12)+t(CH_2)(8)	**ν(^{10}COH)**
ν_{33}	1119 (108,1)0.17	1069	α(C_6-OH)(16)-**α_1(R)(15)**+ν(C_6-OH)(14)-β(C_3-H_8)(14)	**α_1(R)**
ν_{34}	1164 (41,2)0.33	1112	α(C_6-OH)(25)-**β(C_2-H_7)(16)**+ρ(NH_2)(9)	**β(C_2-H_7)**
ν_{35}	1167 (41,6)0.15	1114	ν(C_4-C_{10})(15)+β(C_2-H_7)(15)-**β(C_5-H_9)(13)**-ν(C_{10}-OH)(11)	**β(C_5-H_9)**
ν_{36}	1175 (30,2)0.58	1122	**α(C_6-OH)(16)**-ρ(NH_2)(15)-ρ(CH_2)(11)-β(C_5-H_9)(10)	**α(^{6}COH)**
ν_{37}	1208 (87,14)0.09	1153	**α(C_1-OH)(32)**-ν(C_1-C_2)(17)-β(C_2-H_7)(13)	**α(^{1}COH)**
ν_{38}	1268 (120,3)0.75	1211	**ν(C_1-OH)(24)**+α_1(R)(13)-β(C_3-H_8)(12)+α(C_1-OH)(8)	**ν(^{1}COH)**
ν_{39}	1282 (70,6)0.32	1224	δ(C_{10}-OH)(19)+ν(C_1-OH)(12)+**ρ(NH_2)(12)**-δ(C_{10}-H_{11})(10)	**ρ(NH_2)**
ν_{40}	1303 (145,22)0.06	1244	**β(C_3-H_8)(21)**+ν(C_1-OH)(14)+ν(C_6-OH)(13)-ν(C_2-C_3)(13)	**β(C_3-H_8)**
ν_{41}	1312 (16,4)0.75	1253	**ρ(CH_2)(48)**-ω(CH_2)(22)-ρ(NH_2)(11)	**ρ(CH_2)**
ν_{42}	1344 (2,4)0.71	1284	**δ(C_{10}-H_{11})(17)**-ν(C_6-OH)(10)+ν(C_4-C_5)(10)	**δ(^{10}CH)**
ν_{43}	1363 (34,6)0.29	1302	**δ(C_{10}-H_{11})(35)**+δ(C_{10}-OH)(15)	**δ(^{10}CH)**
ν_{44}	1389 (27,2)0.35	1327	ω(CH_2)(20)+α(C_1-OH)(14)+**ν(C_3-C_4)(12)**+β(C_3-H_8)(9)+ν(C_5-C_6)(8)	**ν(C_3-C_4)**
ν_{45}	1399 (6,3)0.75	1336	**ω(CH_2)(29)**-α(C_1-OH)(9)-ν(C_5-C_6)(8)	**ω(CH_2)**
ν_{46}	1439 (59,15)0.20	1374	**α(C_{10}-OH)(28)**-δ(C_{10}-H_{11})(22)+ν(C_4-C_{10})(11)-ω(CH_2)(10)	**α(^{10}COH)**
ν_{47}	1473 (102,2)0.23	1407	ν(C_5-C_6)(19)-**ν(C_2-C_3)(14)**-ν(C_6-OH)(8)	**ν(C_2-C_3)**
ν_{48}	1494 (5,7)0.58	1427	**σ(CH_2)(91)**	**σ(CH_2)**
ν_{49}	1555 (117,5)0.67	1485	β(C_5-H_9)(13)+**ν(C_1-C_2)(12)**-β(C_3-H_8)(12)-β(C_2-H_7)(11)-ν(C_1-OH)(10)-ν(C_4-C_5)(10)+ν(C_1-C_6)(10)	**ν(C_1-C_2)**
ν_{50}	1646 (26,7)0.75	1572	ν(C_1-C_2)(23)-ν(C_1-C_6)(18)+**ν(C_4-C_5)(15)**-ν(C_3-C_4)(11)	**ν(C_4-C_5)**
ν_{51}	1656 (31,3)0.75	1581	**σ(NH_2)(95)**	**σ(NH_2)**
ν_{52}	1658 (23,49)0.57	1583	**ν(C_5-C_6)(21)**+ν(C_2-C_3)(19)+α_2(R)(11)-ν(C_1-C_6)(10)	**ν(C_5-C_6)**
ν_{53}	2946 (50,128)0.20	2813	**ν(C_{10}-H_{11})(98)**	**ν(^{10}CH)**
ν_{54}	3002 (42,83)0.11	2867	**ν(C_{16}-H_{18})(89)**+ν(C_{16}-H_{17})(10)	**ν(C_{16}-H_{18})**

(*Contd.*)

Table 8 – Calculated vibrational frequencies and proposed assignments for NE conformer C-I. (*Contd.*)

S. No.	Frequencies (cm^{-1})		PEDs	Modes.
	$Unscaled	*Scaled		
ν_{55}	3075 (20,35)0.49	2937	**$\nu(C_{16}$-$H_{17})$(89)**-$\nu(C_{16}$-$H_{18})$(10)	**$\nu(C_{16}$-$H_{17})$**
ν_{56}	3161 (11,63)0.42	3019	**$\nu(C_3$-$H_8)$(93)**	**$\nu(C_3$-$H_8)$**
ν_{57}	3175 (6,57)0.22	3032	**$\nu(C_5$-$H_9)$(99)**	**$\nu(C_5$-$H_9)$**
ν_{58}	3192 (6,153)0.22	3049	**$\nu(C_2$-$H_7)$(93)**	**$\nu(C_2$-$H_7)$**
ν_{59}	3512 (1,183)0.11	3354	**$\nu(N_{21}$-$H_{23})$(67)**+$\nu(N_{21}$-$H_{22})$(33)	**$\nu(N_{21}$-$H_{23})$**
ν_{60}	3594 (7,86)0.61	3432	**$\nu(N_{21}$-$H_{22})$(67)**-$\nu(N_{21}$-$H_{23})$(33)	**$\nu(N_{21}$-$H_{22})$**
ν_{61}	3697 (132,94)0.14	3531	**$\nu(O_{19}$-$H_{20})$(96)**	**$\nu(^{19}OH)$**
ν_{62}	3792 (110,75)0.19	3622	**$\nu(O_{14}$-$H_{15})$(97)**	**$\nu(^{14}OH)$**
ν_{63}	3849 (80,100)0.22	3676	**$\nu(O_{12}$-$H_{13})$(97)**	**$\nu(^{12}OH)$**

Table 9 – Calculated vibrational frequencies and proposed assignments for NE conformer (C-II).

S. No.	Frequencies (cm^{-1})		PEDs	Modes
	$Unscaled	*Scaled		
ν_1	35 (5,2)0.75	34	**$\tau(C_4$-$C_{10})$(83)**	**$\tau(C_4$-$C_{10})$**
ν_2	79 (3,2)0.73	77	**$\gamma(C_4$-$C_{10})$(29)**+$\alpha(C_4$-C_{10}-$C_{16})$(22)+Φ_2(R)(20)	**$\gamma(C_4$-$C_{10})$**
ν_3	114 (5,0)0.75	111	**$\tau(C_{10}$-$C_{16})$(63)**-$\tau(O_{19}$-$H_{20})$(14)+$\beta(C_4$-$C_{10})$(10)	**$\tau(C_{10}$-$C_{16})$**
ν_4	163 (136,3)0.67	160	**$\tau(O_{14}$-$H_{15})$(72)**+$\tau(O_{12}$-$H_{13})$(8)	**$\tau(^{14}OH)$**
ν_5	179 (9,0)0.70	175	Φ_2(R)(39)-**$\alpha(C_4$-C_{10}-$C_{16})$(14)**+Φ_1(R)(8)	**α(CCC)**
ν_6	218 (6,0)0.55	213	**$\beta(C_4$-$C_{10})$(29)**-$\tau(C_{10}$-$C_{16})$(26)+$\tau(O_{19}$-$H_{20})$(8)	**$\beta(C_4$-$C_{10})$**
ν_7	253 (1,1)0.30	248	Φ_3(R)(24)+$\alpha(C_4$-C_{10}-$C_{16})$(14)+**$\gamma(C_6$-OH)(10)**+$\gamma(C_5$-$H_9)$(10)	**$\gamma(^6COH)$**
ν_8	260 (9,1)0.21	255	**$\tau(NH_2)$(67)**-$\tau(O_{19}$-$H_{20})$(20)	**$\tau(NH_2)$**
ν_9	304 (7,1)0.63	297	**$\beta(C_6$-OH)(41)**+$\beta(C_1$-OH)(34)	**$\beta(^6COH)$**
ν_{10}	321 (5,2)0.18	314	**$\alpha(C_{10}$-C_{16}-$N_{21})$(36)**-α_2(R)(9)	**α(CCN)**
ν_{11}	332 (3,3)0.29	325	**$\delta(C_{10}$-OH)(12)**-α_2(R)(12)+$\gamma(C_1$-OH)(9)+$\nu(C_4$-$C_{10})$(9)	**$\delta(^{10}COH)$**
ν_{12}	402 (9,1)0.50	393	**$\gamma(C_1$-OH)(31)**+Φ_1(R)(12)+$\tau(O_{12}$-$H_{13})$(10)+$\alpha(C_4$-C_{10}-$C_{16})$(9)	**$\gamma(^1COH)$**
ν_{13}	412 (64,1)0.74	403	**$\tau(O_{12}$-$H_{13})$(75)**+Φ_3(R)(8)	**$\tau(^{12}OH)$**
ν_{14}	450 (4,1)0.73	440	Φ_3(R)(20)+$\gamma(C_1$-OH)(14)-$\gamma(C_6$-OH)(12)-**$\beta(C_1$-OH)(9)**-Φ_2(R)(9)	**$\beta(^1COH)$**
ν_{15}	467 (3,0)0.49	457	**Φ_3(R)(37)**-$\gamma(C_6$-OH)(14)	**Φ_3(R)**
ν_{16}	535 (12,1)0.71	524	**$\delta(C_{10}$-OH)(24)**-$\alpha(C_{10}$-C_{16}-$N_{21})$(16)+$t(CH_2)$(11)	**$\delta(^{10}COH)$**

(*Contd.*)

Table 9 – Calculated vibrational frequencies and proposed assignments for NE conformer (C-II). (*Contd.*)

S. No.	Frequencies (cm^{-1})		PEDs	Modes
	$^{\$}$Unscaled	*Scaled		
ν_{17}	592 (4,7)0.33	580	**α_3(R)(31)**+β(C_1-OH)(21)+ν(C_1-C_2)(9)	**α_2(R)**
ν_{18}	604 (79,2)0.57	591	**τ(O_{19}-H_{20})(64)**	**τ(^{19}OH)**
ν_{19}	625 (52,1)0.57	612	**α_3(R)(15)**-γ(C_4-C_{10})(9)+Φ_2(R)(9)-τ(O_{19}-H_{20})(9)	**α_3(R)**
ν_{20}	639 (17,2)0.28	626	**Φ_2(R)(22)**-γ(C_4-C_{10})(21)-γ(C_6-OH)(14)	**Φ_2(R)**
ν_{21}	725 (0,1)0.55	710	**Φ_1(R)(56)**-γ(C_6-OH)(17)-γ(C_1-OH)(17)	**Φ_1(R)**
ν_{22}	780 (77,10)0.04	764	ω(NH_2)(14)+**ν(C_6-OH)(11)**+α_1(R)(11)+ν(C_4-C_{10})(8)	**ν(^{6}COH)**
ν_{23}	791 (20,20)0.08	774	ν(C_1-OH)(25)+**ν(C_1-C_6)(22)**+ν(C_1-C_2)(8)	**ν(C_1-C_6)**
ν_{24}	815 (29,0)0.71	797	**γ(C_2-H_7)(50)**+γ(C_3- H_8)(19)+γ(C_1-OH)(8)	**γ(C_2-H_7)**
ν_{25}	826 (51,4)0.37	808	**ω(NH_2)(46)**+ν(C_{10}-C_{16})(10)-t(CH_2)(9)	**ω(NH_2)**
ν_{26}	881 (16,3)0.21	863	**γ(C_5-H_9)(64)**+Φ_1(R)(15)	**γ(C_5-H_9)**
ν_{27}	910 (85,4)0.22	891	ν(C_{10}-OH)(19)-ω(NH_2)(17)+**ν(C_{10}-C_{16})(12)**	**ν(C_{10}-C_{16})**
ν_{28}	942 (3,0)0.41	922	**γ(C_3- H_8)(54)**-γ(C_2-H_7)(25)	**γ(C_3-H_8)**
ν_{29}	964 (9,4)0.09	943	**t(CH_2)(21)**+ν(C_3-C_4)(9)+ρ(NH_2)(9)+ν(C_4-C_{10})(8)	**t(CH_2)**
ν_{30}	970 (6,7)0.69	949	ν(C_{10}-C_{16})(21)+ρ(NH_2)(16)-**ν(C_4-C_{10})(10)**+t(CH_2)(9)	**ν(C_4-C_{10})**
ν_{31}	1057 (22,12)0.23	1009	**ν(C_{16}-N_{21})(76)**	**ν(C_{16}-N_{21})**
ν_{32}	1100 (16,8)0.13	1050	**ν(C_{10}-OH)(31)**-ν(C_4-C_5)(9)-ν(C_{10}-C_{16})(8)	**ν(^{10}COH)**
ν_{33}	1126 (155,3)0.40	1075	ν(C_{10}-OH)(24)-α(C_1-OH)(15)-**α_1(R)(9)**-β(C_3-H_8)(9)	**α_1(R)**
ν_{34}	1165 (29,4)0.46	1113	**β(C_2-H_7)(25)**-ν(C_2-C_3)(18)+α(C_1-OH)(16)-β(C_3-H_8)(11)	**β(C_2-H_7)**
ν_{35}	1167 (15,5)0.11	1115	**ρ(NH_2) (20)**-δ(C_{10}-H_{11})(14)+ρ(CH_2)(12)-α(C_{10}-OH)(8)	**ρ(NH_2)**
ν_{36}	1177 (29,3)0.22	1124	α(C_1-OH)(21)+**β(C_5-H_9)(19)**-ν(C_4-C_{10})(13)	**β(C_5-H_9)**
ν_{37}	1206 (38,4)0.15	1152	**α(C_6-OH)(29)**-ν(C_5-C_6)(17)+β(C_5-H_9)(15)+ν(C_1-OH)(10)	**α(^{6}COH)**
ν_{38}	1266 (81,4)0.67	1209	**α(C_1-OH)(14)**+α_1(R)(12)+ν(C_1-OH)(10)-β(C_2-H_7)(9)	**α(^{1}COH)**
ν_{39}	1287 (19,4)0.61	1229	**δ(C_{10}-H_{11})(15)**+α(C_6-OH)(12)-ν(C_1-OH)(10)+δ(C_{10}-OH)(9)	**δ(^{10}CH)**
ν_{40}	1304 (233,23)0.06	1245	ν(C_6-OH)(25)-ν(C_2-C_3)(16)-ν(C_4-C_5)(11)+**ν(C_1-OH)(10)**-ν(C_1-C_6)(10)	**ν(^{1}COH)**
ν_{41}	1311 (10,5)0.70	1252	**ρ(CH_2)(46)**-ω(CH_2)(24)-ρ(NH_2)(12)	**ρ(CH_2)**
ν_{42}	1342 (79,2)0.41	1282	**β(C_3-H_8)(17)**+β(C_5-H_9)(16)-α(C_6-OH)(16)-α(C_1-OH)(10)	**β(C_3-H_8)**
ν_{43}	1355 (35,3)0.74	1294	**δ(C_{10}-H_{11})(43)**+δ(C_{10}-OH)(13)	**δ(^{10}CH)**
ν_{44}	1386 (44,7)0.06	1323	**ν(C_3-C_4)(15)**+ν(C_1-C_2)(14)-ω(CH_2)(11)-ν(C_4-C_5)(9)	**ν(C_3-C_4)**

(*Contd.*)

Table 9 – Calculated vibrational frequencies and proposed assignments for NE conformer (C-II). (*Contd.*)

S. No.	Frequencies (cm^{-1})		PEDs	Modes
	$^{\$}$Unscaled	*Scaled		
ν_{45}	1394 (13,8)0.38	1331	**$\omega(CH_2)$(34)**+$\alpha(C_{10}$-OH)(12)-$\rho(NH_2)$(10)+$\rho(CH_2)$(8)	**$\omega(CH_2)$**
ν_{46}	1433 (36,12)0.21	1369	**$\alpha(C_{10}$-OH)(31)**-$\delta(C_{10}$-$H_{11})$(22)-$\omega(CH_2)$(10)	**$\alpha(^{10}COH)$**
ν_{47}	1492 (1,4)0.68	1425	$\sigma(CH_2)$(14)-$\nu(C_5$-$C_6)$(13)+**$\nu(C_2$-$C_3)$(11)**-$\nu(C_4$-$C_5)$(10)	**$\nu(C_2$-$C_3)$**
ν_{48}	1495 (5,7)0.51	1428	**$\sigma(CH_2)$(78)**	**$\sigma(CH_2)$**
ν_{49}	1545 (169,2)0.74	1475	$\beta(C_2$-$H_7)$(18)**-$\nu(C_1$-$C_2)$(15)**-$\beta(C_5$-$H_9)$(11)+$\nu(C_3$-$C_4)$(10)	**$\nu(C_1$-$C_2)$**
ν_{50}	1645 (43,10)0.61	1571	$\nu(C_1$-$C_6)$(21)-$\nu(C_1$-$C_2)$(18)-**$\nu(C_4$-$C_5)$(15)**+$\nu(C_3$-$C_4)$(11)	**$\nu(C_4$-$C_5)$**
ν_{51}	1656 (30,3)0.75	1582	**$\sigma(NH_2)$(95)**	**$\sigma(NH_2)$**
ν_{52}	1661 (4,38)0.60	1587	**$\nu(C_5$-$C_6)$(26)**+$\nu(C_2$-$C_3)$(16)+α_2(R)(11)-$\nu(C_3$-$C_4)$(8)	**$\nu(C_5$-$C_6)$**
ν_{53}	2942 (52,126)0.20	2809	**$\nu(C_{10}$-$H_{11})$(98)**	**$\nu(^{10}CH)$**
ν_{54}	3001 (43,85)0.11	2866	**$\nu(C_{16}$-$H_{18})$(90)**+$\nu(C_{16}$-$H_{17})$(9)	**$\nu(C_{16}$-$H_{18})$**
ν_{55}	3076 (19,36)0.48	2938	**$\nu(C_{16}$-$H_{17})$(89)**-$\nu(C_{16}$-$H_{18})$(10)	**$\nu(C_{16}$-$H_{17})$**
ν_{56}	3151 (18,109)0.31	3009	**$\nu(C_2$-$H_7)$(98)**	**$\nu(C_2$-$H_7)$**
ν_{57}	3172 (4,86)0.25	3029	**$\nu(C_5$-$H_9)$(99)**	**$\nu(C_5$-$H_9)$**
ν_{58}	3211 (1,77)0.20	3067	**$\nu(C_3$-$H_8)$(98)**	**$\nu(C_3$-$H_8)$**
ν_{59}	3512 (1,182)0.11	3354	**$\nu(N_{21}$-$H_{23})$(67)**+$\nu(N_{21}$-$H_{22})$(33)	**$\nu(N_{21}$-$H_{23})$**
ν_{60}	3595 (7,86)0.60	3433	**$\nu(N_{21}$-$H_{22})$(67)**-$\nu(N_{21}$-$H_{23})$(33)	**$\nu(N_{21}$-$H_{22})$**
ν_{61}	3699 (130,93)0.14	3532	**$\nu(O_{19}$-$H_{20})$(96)**	**$\nu(^{19}OH)$**
ν_{62}	3793 (111,75)0.19	3623	**$\nu(O_{12}$-$H_{13})$(97)**	**$\nu(^{12}OH)$**
ν_{63}	3852 (89,127)0.23	3679	**$\nu(O_{14}$-$H_{15})$(97)**	**$\nu(^{14}OH)$**

The numbers (in bracket) after the modes are the % potential energy calculated using normal coordinate analysis.

$^{\$}$: The first and second numbers within each bracket represent IR intensity (km/mol) and Raman intensity while the number before each bracket represents the corresponding calculated frequency (cm^{-1}), first word after each bracket represent corresponding depolarization ratios of the Raman band.

***:**Calculated wavenumbers below 1000 cm^{-1} were scaled by the scale factor 0.9786 and those above 1000 cm^{-1} by the scale factor 0.9550 for larger wavenumbers.

The abbreviations are- ν = stretching, ω = wagging, τ = torsion, t = twisting, ρ = rocking, σ = scissoring, δ = deformation, α = planar deformation of ring, β = planar deformation, γ = non-planar deformation, Φ=non-planar deformation of ring. The mode in bold letters in the PEDs column corresponds to the assigned mode.

bending modes. Most of the stretching C-H modes do not show much variation in going from conformer C-I to conformer C-II however, some of the modes show small variations in magnitudes. The in-phase and out-of-phase C-H stretching modes are found to have magnitudes 3049/3067 and 3019/3009 cm^{-1} and similarly, the in-phase and out-of-phase C-H deformation modes are calculated to be 806/920 and 922/797 cm^{-1} in conformers C-I/C-II. The C_5-H bond gives rise to the stretching (7b) and non-planar bending modes (5) at 3032/3029 and 858/863cm^{-1} in C-I/C-II. All the same, the C-H bonds of the phenyl ring participate together with in the three planar C-H bending modes. The planar C-H deformation mode corresponding to the mode 3 (1350 cm^{-1}) of benzene in which all the C-H band in phase is found at

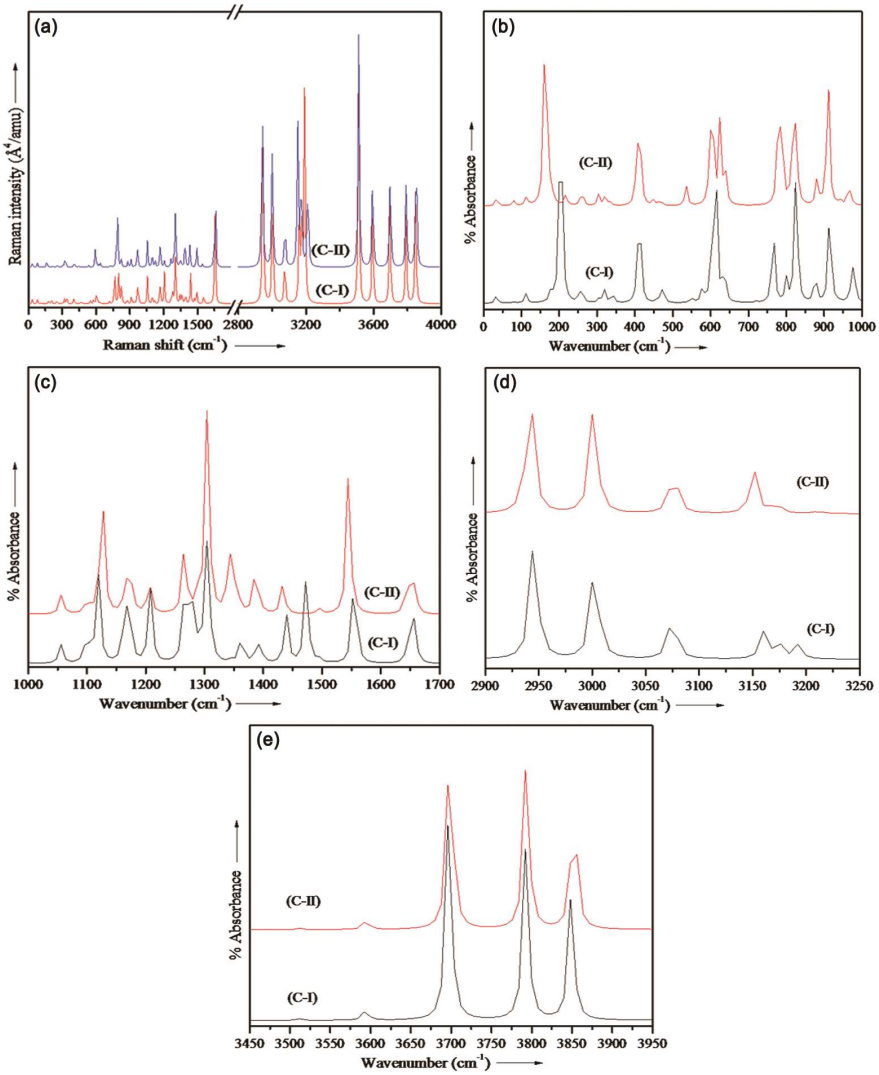

Fig. 7 – Calculated IR spectrum for two low energy NE conformers.

~1244/1282 cm^{-1} in conformers C-I/C-II. The other two ring planar C-H deformations (18a, 9b) are calculated to have magnitudes 1112/1113 and 1114/1124 cm^{-1} in conformers C-I/C- II. The corresponding β(C-H) modes (18a, 9b) were computed at 1068/1071/1125/1012 and 1114/1115/1003/1143cm^{-1} and observed modes correspond to 18a at the frequencies 1112/1163/ 1079/1037 cm^{-1} in NE/E/Dopamine/Bz [36/28/15/32].

Out of three γ(C-H) modes, one of the three modes shows a small variation while the other two modes (10b, 17b) have the larger variation in going from the conformer C-I to C-II. Similarly, Out of three ν(C-H) modes, 2 of the 3 modes show a larger variation. The mode 20b is found at lower wavenumber whereas reverse order has been found for the mode 2 in going from the conformer C-I to C-II. The side chain bond ^{10}CH has two deformations (δ) and stretching (ν) modes. Out of the three, 2 deformations modes are found at the frequencies 1284/1229 and 1302/1294 cm^{-1} in conformers C-I/C-II. The mode (ν_{42}) is found at the lower magnitude in comparison the MIPA. All the three side chain ^{10}CH modes have been reduced in magnitude in going from conformer C-I to C-II in which the stretching mode has been smaller by ~ 35 cm^{-1} in comparison to MIPA.

3.6.3 O-H/C-O(H) group modes (18 modes)

The stretching vibration of the O-H group consists in the region 3200-3600 cm^{-1}. For 5-HT, Jha *et al.*[37] have assigned the ν(O-H) mode at ~ 3667 cm^{-1}. In the present case, the computed frequencies 3531/3532(ν_{61}), 3622/3623(ν_{62}) and 3676/3679(ν_{63}) cm^{-1} correspond to the side chain, bonded and non-bonded O-H stretching modes, respectively. The computed

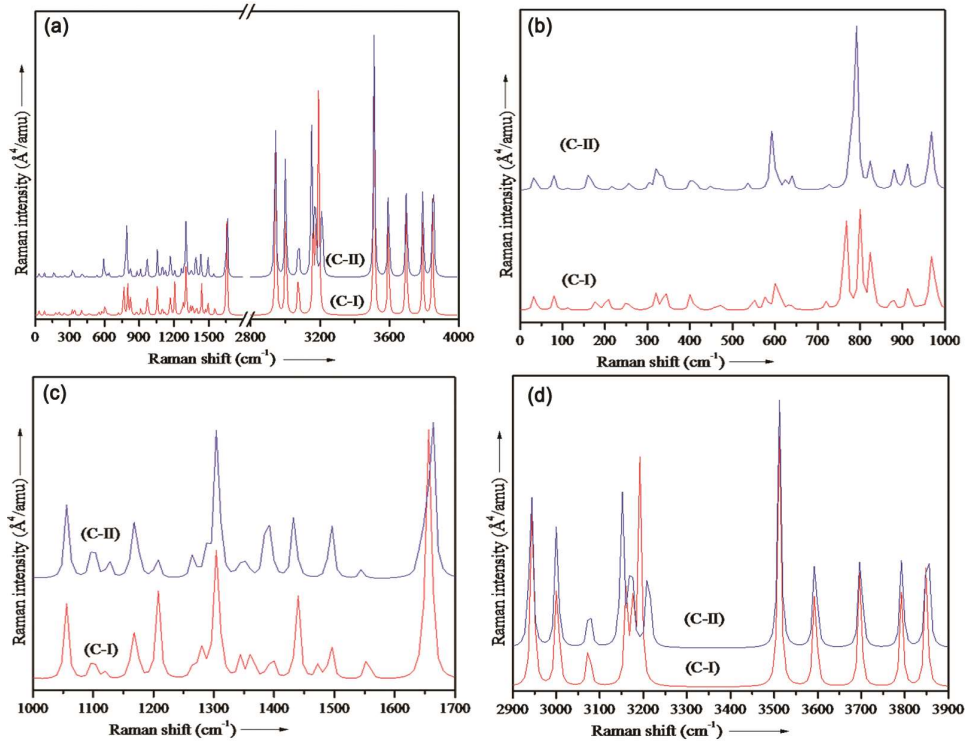

Fig. 8 – Calculated Raman spectra for two low energy NE conformer.

Table 10 – The unscaled computed and observed modes of the NE, E, DOPA, o-DHB, Bz and MIPA molecules.

S. No	NE				E			DOPA			1,2-DHB			Bz/MIPA			Modes
	Calc.		Obsd [a]		Calc	Obsd [b]		Calc	Obsd [c]		Calc	Obsd [d]		Calc	Obsd [e, f]		
	C-I	C-II	IR	R		IR	R		IR	R		IR	R		IR	R	
ν_1	34	35	-	-	30	-	-	35	-	-	-	-	-	133	-	-	τ(CC)
ν_2	81	79	-	-	63	-	85	75	-	58	-	-	-	-	-	-	γ(CC)
ν_3	111	114	-	-	80	-	102	129	-	90	-	-	-	268	-	-	τ(CC)
ν_4	179	179	-	-	219	-	196	191	-	200	-	-	-	378	-	-	α(CCC)
ν_5	204	163	-	-	200	-	-	406	-	389	163	-	-	-	-	-	non-bonded τ(OH)
ν_6	206	218	-	-	198	-	-	295	-	-	-	-	-	-	-	-	β(CC)
ν_7	250	253	-	-	158	-	256	243	-	-	194	-	202	-	-	-	non-bonded γ(COH)
ν_8	259	260	-	-	-	-	-	272	-	261	-	-	-	244	-	-	τ(NH_2)
ν_9	307	304	-	-	308	-	316	310	-	306	292	-	295	-	-	-	non-bonded β(COH)
ν_{10}	320	321	-	-	356	-	297	430	-	-	-	-	-	637	-	-	α(CCN)
ν_{11}	341	332	-	-	275	-	364	-	-	-	-	-	-	-	-	-	side chain δ(COH)
ν_{12}	401	402	-	-	407	-	-	366	-	326	392	-	-	-	-	-	bonded γ(COH)
ν_{13}	412	412	-	-	413	-	-	172	-	153	411	-	-	-	-	-	bonded τ(OH)
ν_{14}	461	467	-	-	460	-	-	455	459	453	457	449	-	409	404	-	16b

(*Contd.*)

Table 10 – The unscaled computed and observed modes of the NE, E, DOPA, o-DHB, Bz and MIPA molecules. (*Contd*.)

S. No	NE				E			DOPA			1,2-DHB			Bz/MIPA			Modes
	Calc.		Obsd [a]		Calc	Obsd [b]		Calc	Obsd [b]		Calc	Obsd [d]		Calc	Obsd [e, f]		
	C-I	C-II	IR	R		IR	R		IR	R		IR	R		IR	R	
ν_{15}	475	450	-	-	484	-	462	473	474	475	448	-	-	-	-	-	bonded β(COH)
ν_{16}	549	535	-	-	555	527	-	-	-	-	-	-	-	426	-	-	side chain δ(COH)
ν_{17}	578	592	-	-	575	-		593	598	591	590	564	564	622	-	606	6b
ν_{18}	603	625	612	-	603	610	591	527	-	-	559	-	-	622	-	606	6a
ν_{19}	613	604	-	-	590	-	-	-	-	-	-	-	-	321	-	-	side chain τ(OH)
ν_{20}	636	639	649	-	639	629	613	641	-	633	568	555	-	409	404	-	16a
ν_{21}	719	725	689	-	719	733	721	728	724	719	718	-	-	719	707	-	4
ν_{22}	765	780	-	-	760	983	985	1308	-	-	1265	-	-	-	-	-	non-bonded ν(COH)
ν_{23}	801	791	-	-	797	779	781	791	750	744	779	769	752	1011	-	993	1
ν_{24}	823	942	-	-	829	818	812	828	814	809	746	722	719	686	673	-	10b
ν_{25}	827	826	-	-	-	-	-	836			-	-	-	837	834	-	$\omega(NH_2)$
ν_{26}	876	881	-	-	879	866	870	850	-	-	958	-	963	863	-	990	5
ν_{27}	915	910	-	-	900	889		717	-	-	-	-	-	802	748	-	ν(CC)
ν_{28}	940	815	-	-	942	943	947	948	-	-	916	916	910	980	967	-	17b
ν_{29}	966	964	-	949	1034	-	-	1046	1013	1011	-	-	-	946	-	-	$t(CH_2)$
ν_{30}	978	970	-	-	901	-	-	892	876	871	-	-	-	931	-	-	ν(CC)
ν_{31}	1056	1057	-	-	962	-	-	1096	-	-	-	-	-	1066	1057	-	ν(CN)
ν_{32}	1100	1100	-	-	1088	-		-	-	-	-	-	-	1142	1126	-	side chain ν(COH)
ν_{33}	1119	1126	1105	-	990	1065	1064	971	945	941	861	859	-	1022	1010	-	12
ν_{34}	1164	1165	-	1112	1118	1163	1163	1121	1079	-	1178	-	-	1060	1037	1060	18a
ν_{35}	1167	1177	-	-	1166	-	-	1168	1114	-	1050	-	-	1197	-	1178	9b
ν_{36}	1175	1206	-	-	1169	-	1103	1179	-	1139	1166	-	-	-	-	-	non-bonded α(COH)
ν_{37}	1208	1266	-	1155	1207	1137	1138	1209	1145	-	1204	1165	1164	-	-	-	bonded α(COH)
ν_{38}	1268	1304	1175	1177	1274	-	-	1272	1206	1204	1298	-	-	-	-	-	bonded ν(COH)
ν_{39}	1282	1167	-	-	-	-	-	1154	-	1109	-	-	-	1191	1126	-	$\rho(NH_2)$
ν_{40}	1303	1342	-	-	1303	1254	-	1348	1284	1282	1357	1281	1276	1381	1350	-	3
ν_{41}	1312	1311	-	1256	1288	-	1259	1333	-	-	-	-	-	-	-	-	$\rho(CH_2)$
ν_{42}	1344	1287	-	-	1335	-	-	-	-	-	-	-	-	1436	1337	-	$\delta(^{10}CH)$
ν_{43}	1363	1355	-	1310	1371	-	-	-	-	-	-	-	-	1379		-	$\delta(^{10}CH)$
ν_{44}	1389	1386	-	-	1394	-	1348	1392	1320	1316	1391	1324	-	1337	1309	-	14
ν_{45}	1399	1394	-	-	1356	1359	-	1415	1341	1350	-	-	-	1418	1337	-	$\omega(CH_2)$
ν_{46}	1439	1433	1350	1346	1436	1205	1198	-	-	-	-	-	-	1269	-	-	side chain α(COH)
ν_{47}	1473	1492	-	1409	1474	1459	1464	1471	1392	1389	1504	-	-	1510	1482	-	19b
ν_{48}	1494	1495	-	-	1502	1406	1405	1508	1460	-	-	-	-	1504	-	-	$\sigma(CH_2)$
ν_{49}	1555	1545	1496	1488	1555	1499	1498	1554	1498	1491	1540	1469	1477	1510	1482	-	19a
ν_{50}	1646	1645	-	1567	1646	1599	1610	1644	1583	1579	1651	-	-	1634	-	1599	8b
ν_{51}	1656	1656	-	-	-	-	-	1657	1615	-	-	-	-	1647	-	-	$\sigma(NH_2)$
ν_{52}	1658	1661	-	-	1668	1631	1632	1655	1599	1596	1647	1597	1604	1634	-	1599	8a
ν_{53}	2946	2942	-	-	2942	-	-	-	-	-	-	-	-	2982	-	-	$\nu(^{10}CH)$
ν_{54}	3002	3001	-	-	2970	-	-	2950	2821	-	-	-	-	2910	-	-	$\nu_s(CH_2)$

(*Contd*.)

Table 10 – The unscaled computed and observed modes of the NE, E, DOPA, o-DHB, Bz and MIPA molecules. (*Contd*.)

S. No	NE				E			DOPA			1,2-DHB			Bz/MIPA			Modes
	Calc.		Obsd [a]		Calc	Obsd [b]		Calc	Obsd [b]		Calc	Obsd [b]		Calc	Obsd [b]		
	C-I	C-II	IR	R		IR	R		IR	R		IR	R		IR	R	
ν_{55}	3075	3076	-	-	3058	2930	2929	3050	-	-	-	-	-	3038	2946	-	$\nu_{as}(CH_2)$
ν_{56}	3161	3211	3000	-	3160	3070	3076	3164	-	3023	3175	-	-	3165	3064	-	20b
ν_{57}	3175	3172	3023	3024	3175	-	-	3150	-	-	3151	-	-	3156	-	3056	7b
ν_{58}	3192	3151	3035	3047	3192	-	-	3191	3035	3054	3198	3052	3056	3192	-	3073	2
ν_{59}	3512	3512	-	-	-	-	-	3499	3145	-	-	-	-	3509	3432	-	$\nu_s(NH_2)$
ν_{60}	3594	3595	-	-	-	-	-	3577	3215	-	-	-	-	3587	3446	-	$\nu_{as}(NH_2)$
ν_{61}	3697	3699	3351	-	3695	3315	-	-	-	-	-	-	-	3826	3653	-	side chain ν(OH)
ν_{62}	3792	3793	3368	-	3793	3376	-	3794	3341	3341	3794	3326	3330	-	-	-	bonded ν(OH)
ν_{63}	3849	3852	-	-	3849		-	3849	3391	-	3853	3450	3463	-	-	-	non-bonded ν(OH)

[a-11, b-28, c-15, d-36, e- 32, f-38]
IR-Infra-red intensity, R- Raman Intensity

frequencies for the bonded and non-bonded ν(O-H) modes of the NE molecule are very close to those of E, dopamine, and 1, 2-DHB; while for the side chain ν(O-H) frequency is found to be computedfrequency 3654 cm^{-1} in MIPA and which is lower by ~32 cm^{-1} from observed frequency[38]. The computed frequencies 200/160(ν_5), 403/403(ν_{13}), and 600/591(ν_{19}) cm^{-1} are assigned to the torsional modes about the non-bonded, bonded and side chain O-H bond for the NE conformers C-I/C-II. The modes ν_5, ν_{13}, ν_{19}, ν_{61}, ν_{62} and ν_{63} seem to be extremely localized modes. From the above discussion, it can be seen that the stretching frequency due to the non-bonded O-H mode is greater than the bonded O-H whereas reverse order is noticed for torsional frequencies. This could be explicated in terms of the intra-molecular H bonding between the bonded O and H atoms. This causes a slight increase in the O_{14}-H_{15} bond length, which decreases the effective stretching force constant, which in becoming reduces the stretching frequency. Then again, the intra-molecular H bonding between the atoms O_{12} and H_{15} gives rise more resistance against the torsional modes, which effectively raises the torsional force constant and thereby lifts the torsional frequencies.

For the conformers C-I and C-II, the computed frequencies 1122/1152(ν_{36}), 1153/1209(ν_{37}) and 1374/1369(ν_{46}) cm^{-1} correspond to the non-bonded, bonded and side chain α (COH) vibrations and the calculated frequencies 749/764(ν_{21}), 1050/1050(ν_{32}) and 1211/1245(ν_{38}) cm^{-1} correspond to the non-bonded, side chain and bonded ν(C-OH) vibrations. Form the PEDs Tables 8 and 9 one can see that for the mode ν (^{1}C-OH) couples with the (^{1}COH) mode along with several other modes, whereas for the mode ν (^{6}C-OH) couples only with several other modes.

The wavenumbers ν_7, ν_9, ν_{11}, ν_{12}, ν_{15} and ν_{16} correspond to bonded, non-bonded and side chain deformation modes of the three (C-OH) groups. Presently, the calculated wavenumbers 245/248, 393/393 and 537/524 cm^{-1} are correlated to the two non-planar and a side chain deformation γ(C-OH) modes whereas the frequencies 300/297, 464/440 and 333/325 cm^{-1} are assigned to the two planar and a side chain deformation β(C-OH) modes, respectively, in conformers C-I and C-II.

3.6.4 NH_2 group modes (6 modes)

The $\nu_s(\nu_{59})$ and $\nu_{as}(\nu_{60})$ modes of the NH_2 group satisfy the empirical relation given by Bellamy and Williams[39] for the two low energy conformers of NE suggesting equivalent nature of the two NH bonds of the NH_2 group. For the NH_2 group the modes ν_s, ν_{as}, σ, ω, and torsional mode (t) of the NH_2 group do not show significant variations while the rocking mode shows a large variation ~ 109 cm^{-1} in going form conformer C-I to C-II. The modes ν_s, ν_{as}, and σ are expected to be localized and pure group modes whereas the remaining modes could be coupled with other normal modes.

3.6.5 CH_2 group modes (6 modes)

Similar to the NH_2 group, it should be noted that the modes $\nu_s(CH_2)(\nu_{54})$ and $\nu_{as}(CH_2)(\nu_{55})$ modes have magnitudes close to 2867 and 2937 cm^{-1} for the

conformers C-I and C-II. The modes $\sigma(CH_2)(\nu_{48})$ $\omega(CH_2)(\nu_{45})$ and $\rho(CH_2)(\nu_{41})$ have been found to have frequencies close to 1427, 1331 and 1252 cm^{-1} for the conformers C-I and C-II. The twisting modes of the CH_2 group have the magnitude 946 cm^{-1} for C-I and are reduced to 943 cm^{-1} for the conformer C-I.

The modes ω, σ, ν_s, and ν_{as} are found to have the unchanged magnitude in going from conformer C-I to the conformer C-II; while the twisting modes and $\rho(CH_2)$ mode are found to have reduced magnitudes (~3 and 5 cm^{-1}) in going from the conformer C-I to C-II. The mode ν_{48} is purely localized and depolarized mode whereas the mode ν_{41} is coupled with other modes of vibration in NE molecules. The modes ν_{29} and ν_{45} are coupled with other modes of vibration.

3.6.6 C_{10}-C_{16}-N_{21} chain modes (6 modes)

For benzene and its amino derivatives, the side chain C-NH_2 stretching frequency seems in the range[32,39] 1000-1300 cm^{-1}. The side chain C_{10}-C_{16}-N_{21} produces six modes as the ν (C_{10}-C_{16}), ν (C_{16}-N_{21}), α (C_4-C_{10}-C_{16}), α(C_{10}- C_{16}-N_{21}), a torsional mode about the C_4-C_{10} bond and another torsional mode about the C_{10}-C_{16} bond. The ν (C_{10}-C_{16}) (ν_{27}) mode shows a small variation of ~ 4 cm^{-1} in going from the conformers C-I to C-II. The angle bending mode $\alpha(C_4$-C_{10}-$C_{16})$ and $\alpha(C_{10}$-C_{16}-$N_{21})$ have same magnitude (~175 & 313 cm^{-1}) for the conformers C-I and C-II. The torsional mode about the C_4-C_{10} bond is close to the one conformer to the other conformer and has been enhanced in magnitude by ~1 cm^{-1} in going from the conformer C-I to C-II. The torsional mode (ν_3) about the C_{10}-C_{16} bond has differed in magnitude by ~ 2 cm^{-1} for the conformers C-I (109 cm^{-1}) and C-II (111 cm^{-1}). This mode (ν_3) is found at the lower wavenumber in comparison to MIPA (262 cm^{-1}). The stretching mode of the C_{16}-N_{21} bond has been computed frequency 1008 and 1009 cm^{-1} for the conformers C-I and C-II, which is found at higher wavenumber in comparison to E.

3.6.7 C_4-C_{10} Linkage modes (3 modes)

The C_4-C_{10} linkage is the bond connecting the 1, 2-DHB and MIPA moieties to each other. With the C_4-C_{10} linkage, a stretching bond ν (C_4-C_{10}), an in-plane bending $\beta(C_4$-$C_{10})$ and out-of-plane bending deformations $\gamma(C_4$-$C_{10})$ of the whole 1,2-DHB moiety with respect to the MIPA moiety.

The ν(C-C) vibration was assigned at the frequency 868 cm^{-1} in N, N-DMT by Vidak *et al*.[40] In the present case, the mode $\nu(C_4$-$C_{10})$ has magnitude 958 cm^{-1} for the conformer C-I; while its magnitude is reduced by ~ 9 cm^{-1} for the conformer C-II. Similarly, for the γ mode corresponding to the C_4-C_{10} bond has the same magnitude (79 cm^{-1}) for the conformer C-I while for C-II it has the somewhat lower magnitude (77 cm^{-1}); whereas the β mode (ν_6) of C_4-C_{10} linkage show variation of ~12 cm^{-1} between the conformer C-I and C-II. This mode (ν_6) is somewhat higher magnitude (194 cm^{-1}) from E while it is significantly lower magnitude (289 cm^{-1}) from dopamine molecule.

4 Conclusions

Comparative vibrational and structural investigations of the two low energy conformers of norepinephrine molecule have been carried out at the B3LYP/6-311++G** level. Out of the 11 possible conformers, 2 conformers have been found up to room temperature. The bond lengths and angles do not express the significant variations while the dihedral angles vary significantly variations in going from conformer C-I to C-II. Some of the vibrational modes of the benzene moiety are conformation-dependent to some extent whereas most of the normal modes of vibration of the MIPA side chain vary significantly in going from conformer C-I to conformer C-II.

Due to strong O-H……N interaction the side chain O-H (0.971Å) and C-O bond lengths have been found larger than the bonded and non-bonded O-H and C-O length whereas the bond angle α(C-O-H) (104.9°) has been found lower than the bonded and non-bonded angle α(C-O-H). The torsional frequency; due to the non-bonded O-H is lower than that due to the bonded O-H. Due to strong O-H……N interaction, the side chain τ(C-O(H)) frequency is higher than bonded and non-bonded τ(C-O(H)) frequencies whereas reverse order is noticed for ν(OH) stretching frequencies. The MEP for the two lowest energy conformers suggested that the sites of the maximum positive and negative ESP vary on changing the conformation that means the reactive sites for different conformers are dissimilar. The atomic charges also change significantly from one conformer to other. The three -OH stretching vibrations are highly localized modes. The τ (O-H) for conformer C-II has the same order of magnitudes (~160 and 403 cm^{-1}) as compared to 1,2-DHB (~160 and 402 cm^{-1}). This is an evidence of the inter-molecular H bonding with the O atom. The non-bonded τ(C-O(H)), γ(COH), ν(CC), $\rho(NH_2)$, α(COH) and $\nu_s(CH_2)$ modes of norepinephrine have been found at higher frequencies, whereas β(CC), α(CCN), $t(CH_2)$ and ν(CN) have been found at

lower frequencies in going from dopamine to norepinephrine.

The planar ring deformation and trigonal bending modes of norepinephrine have been found at higher frequencies in comparison to dopamine. From the Williams and Bellamy empirical relation, the nature of the two NH bonds of the NH_2 group is different. The computations of the HOMO and LUMO energies of NE conformers in the ground state have been carried out. The value of energy gap, ~ 5.431 eV, indicates it to be a soft molecule. The HOMO-LUMO energy gap endorses the pharmacological active property of norepinephrine. The molecular electrostatic potential (MEP) shows that the positive potential sites are about the H atoms and the negative potential sites are delivered at the electronegative atoms. The MEP surface suggests that the sites close to the O_{14} (C-I), O_{12} (C-II) and O_{19} atoms of the side chain are regions of the most negative ESP and the sites close to the H_{13}, H_{15} and N_{21} atoms (C-I and C-II) are regions of the most positive ESP.

References

1 Hardmaman J G, Limbird L E & Molinoff P B, *Goodman Gilmans*; *the pharmacological basis of therapeutics*, 9th Eds; (McGraw-Hill: New York), 1996.
2 Bergin R & Carlstrom D, Acta Cryst, B24 (1968) 1506.
3 Bustard T M & Egan R S, *Tetrahedron*, 27 (1971) 4457.
4 Pullman B & Courriere P, *Quantum mechanics of molecular conformation*, B Pullman Ed, (John Wiley & Sons), (1976) 547.
5 Alagona G & Ghio C, *Int J Quantum Chem*, 90 (2002) 641.
6 Nagy P I, Alagona G & Ghio C & Takacss-Novak K, *J Am Chem Soc*, 125 (2003) 2770.
7 Snock L C, Van Mourik T & Simons J P, *Mol Phys*, 101 (2003) 1239.
8 Snock L C, Van Mourik T, Carcabal P & Simons J P, *Phys Chem Chem Phys*, 5 (2003) 4519.
9 Van Mourik T & Fruchtl H A, *Mol Phys*, 103 (2005) 1641.
10 Van Mourik T, *Chem Phys Lett*, 414 (2005) 364.
11 Park M K, Yoo H S, Kang Y K & Lee N S, *Bull Korean chem Soc*, 13 (1992) 230.
12 Benoit D M, *J Chem Phys*, 129 (2008) 234334.
13 Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, Scalmani G, Barone V, Mennucci B, Petersson G A, Nakatsuji H, Caricato M, Li X, Hratchian H P, Izmaylov A F, Bloino J, Zheng G, Sonnenberg J L, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery J A, Peralta J E, Ogliaro F, Bearpark M, Heyd J J, Brothers E, Kudin K N, Staroverov V N, Keith T, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant J C, Iyengar S S, Tomasi J, Cossi M, Rega N, Millam J M, Klene M, Knox J E, Cross J B, Bakken V, Adamo C Jaramillo, J, Gomperts R, Stratmann R E, Yazyev O, Austin A J, Cammi R, Pomelli C, Ochterski J W, Martin R L, Morokuma K, Zakrzewski V G, Voth G A, Salvador P, Dannenberg J J, Dapprich S, Daniels A D, Farkas O, Foresman J B, Ortiz J V, Cioslowski J, Fox D J, Gaussian 09, Revision B01, Gaussian, Inc, Wallingford CT, 2010.
14 Dennington R, Keith T & Millam J, GaussView, Version 412, Semichem Inc, Shawnee Mission, KS, 2007.
15 Jha O, Yadav T K & Yadav R A, *Spectrochim Acta A*, 189 (2018) 473.
16 Rauhut G & Pulay P, *J Phys Chem*, 99 (1995) 3093.
17 Andersen A M, *Acta Chem Scand B*, 29 (1975) 239.
18 Marstokk K M & Mqllendal H, *J Mol Struc*, 35 (1976) 57.
19 Sato H, Dybal J, Murakami R, Noda I & Ozaki Y, *J Mol Struct*, 35 (2005) 744.
20 Meenakshi R, *Mol Simulat*, 36 (2010) 425.
21 Dewar M J S, *The molecular orbital theory of organic chemistry*, (McGraw-Hill and Inc), (1969).
22 Coulson C A & McWeeny R, Coulson's Valence Oxford University Press, 1979.
23 Pir H, Günay N, Avcı D & Atalay Y, *Spectrochim Acta A*, 96 (2012) 916.
24 Padmaja L, Ravi Kumar C, Sajan D, Joe I H, Jayakumar V S & Pettit G R, *J Raman Spectrosc*, 40 (2009) 419.
25 Sagdinc S & Pir H, *Spectrochim Acta A*, 73 (2009) 181.
26 Politzer P & Murray J S, *Theor Chem Acc*, 108 (2002) 134.
27 Okulik N & Jubert A H, *J Mol Des*, 4 (2005) 17.
28 Gunasekaran S, Thilak K R & Ponnusamy S, *Indian J Pure Appl Phys*, 45 (2007) 884.
29 Yadav R A & Singh I S, *The J Sci Res*, 33 (1982-83) 133.
30 Frisch A, Nielsen A B, Holder A J, Gauss View user manual, Gaussian, Inc, Pittsburgh, PA, 2000.
31 Martin J M L, Alsenoy V & Alsenoy C V, GAR2PED, University of Antwerp, 1995.
32 Varsanyi G, *Vibrational spectra of benzene derivatives*, (Academic Press: New York), 1969.
33 Ikezawa Y, Yoshida A & Sekiguchi R, *Electrochim Acta*, 46 (2001) 769.
34 Pulay P, Fogarasi G, Pang F & Boggs J E, *J Am Chem Soc*, 101 (1979) 2550.
35 Silverstein M, Clayton B G & Morill C, *Spectometric identification of organic compounds*, (Wiley: New York), 1981.
36 Ramirez F J & Lopez Navarrete J T, *Vibrat Spectrosc*, 4 (1993) 321.
37 Jha O, Yadav T K & Yadav R A, *Spectrochim Acta A*, 173 (2017) 307.
38 Cacela C, Fausto R & Duarte L, *Vibrational Spectrosc*, 26 (2001) 113.
39 Bellamy L J & Williams R L, *J Chem Soc*, (1956) 2753.
40 Vidak A, Sapic I M & Dananic V, *Integr Mol Med*, 2 (2015) 354.